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Health and Environmental Effects Profile for Propylene Oxide

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR PROPYLENE OXIDE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
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16. ABSTRACT

The Health and Environmental Effects Profile for propylene oxide was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Propylene oxide has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for propylene oxide is 2.39×10^{-2} $(mg/kg/day)^{-1}$ for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for propylene oxide is 1000.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
BOD	Biochemical oxygen demand
BODT	Biochemical oxygen demand theoretical
bw	Body weight
CNS	Central nervous system
CS	Composite score
DNA	Deoxyribonucleic acid
K_{oc}	Soil sorption coefficient
K_{ow}	Log Octanol/Water Partition Coefficient
K_w	Water-to-air ratio
LC_{50}	Contentration lethal to 50% of recipients
LC_{low}	Lowest lethal concentration
LD_{50}	Dose lethal to 50% of recipients
MED	Minimum effective dose
MTD	Maximum tolerated dose
MW	Molecular weight
ppm	Parts per million
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
T	Temperature
THF	Tetrahydrofuran
TLV	Threshold limit value
TWA	Time-weighted average

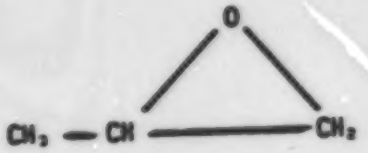
LIST OF ABBREVIATIONS (cont.)

UV	Ultraviolet
VP	Vapor pressure
WS	Water solubility
v/v	Volume per volume

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The chemical commonly known as propylene oxide is also known by the synonyms methyloxirane, 1,2-epoxypropane, PO and propene oxide. The structure, molecular weight, and empirical formula for propylene oxide are as follows:



Molecular weight: 58.08

Empirical formula: C_3H_6O

The CAS Registry number for propylene oxide is 75-56-9.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Propylene oxide is a colorless liquid with a sweet characteristic odor (Verschueren, 1983). Selected physical properties are listed below:

Freezing point:	-112°C	Kirk and Dempsey (1982)
Boiling point (760 torr):	34.2°C	Kirk and Dempsey (1982)
Flash point:	< -20°C	Kirk and Dempsey (1982)
Index of refraction (25°C):	1.36322	Kirk and Dempsey (1982)
Specific gravity (20°C):	0.830	Kirk and Dempsey (1982)
Vapor pressure, mm Hg:		
at 0°C	181	Kirk and Dempsey (1982)
at 10°C	295	Kirk and Dempsey (1982)
at 20°C	440	Kirk and Dempsey (1982)
at 30°C	646	Kirk and Dempsey (1982)
at 25°C	538	Bogyo et al. (1980)
at 25°C	543	Gallant (1967)

Water solubility:		
at 20°C	405,000 ppm	Verschueren (1983)
at 30°C	650,000 ppm	Verschueren (1983)
at 25°C	59%	Bogyo et al. (1980)
at 20°C	33 parts/100 parts	Perry and Chilton (1973)
K_{ow}:	0.03	Hansch and Leo (1981)
Conversion factors:	1 mg/m³ = 0.421 ppm	Verschueren (1983)
	1 ppm = 2.37 mg/m³	Verschueren (1983)

Propylene oxide is miscible with most organic solvents. It can exist as two optical isomers, but the racemic mixture is the commercial product (Kirk and Dempsey, 1982).

Propylene oxide exhibits a high degree of chemical reactivity because of the presence of the oxirane ring (Kirk and Dempsey, 1982). Propylene oxide reacts with water to form propylene glycol, and it is readily polymerized by alkaline catalysts to form polyether polyols. Organic acids react with propylene oxide to yield the propylene glycol esters. In addition, propylene oxide can participate in a variety of other types of chemical reactions.

1.3. PRODUCTION DATA

The current manufacturers of propylene oxide, along with their respective locations and annual capacities, are listed in Table 1-1. Production data for 1977, available from the U.S. EPA TSCA Production File (U.S. EPA, 1977), is listed in Table 1-2. The most recent production figures available from the United States International Trade Commission (USITC, 1979, 1980, 1981) are as follows:

Year	Production (millions of pounds)
1980	1767
1979	2249
1978	2047

TABLE 1-1

Current Manufacturers of Propylene Oxide*

Manufacturer/Location	Annual Capacity (millions of pounds)
ARCO Chemical Co. (Atlantic-Richfield)	
Bayport, TX	1020
Channelview, TX	400
Dow Chemical Co.	
Freeport, TX	950
Plaquemine, LA	400
Total	2770

*Source: SRI, 1984; CMR, 1984

TABLE 1-2

Production Data .or Propylene Oxide as Shown by the 1977 TSCA Production File*

Company/Location	Type	Annual Production Range (lbs)
Olin Corp.		
Brandenburg, KY	manufacturer	50-100 million
Dow Chemical		
Freeport, TX	manufacturer	confidential
Plaquemina, LA	manufaturer	100-500 million
Oxirane Chemical		
Pasadena, TX	manufacturer	500-100 million
Channelview, TX	manufacturer	50-100 million
BASF Wyandotte		
Wyandotte, MI	manufacturer	confidential
Jefferson Chemical		
Fort Neches, TX	manufacturer	confidential

*Source: U.S. EPA, 1977

In 1983, 166 million pounds of propylene oxide were exported (U.S. Department of Commerce, 1984a), while 32 million pounds were imported (U.S. Department of Commerce, 1984b).

The Dow Chemical plants in Freeport, TX, and Plaquemine, LA, manufacture propylene oxide using the chlorohydrin process (Kirk and Dempsey, 1982). This process involves the reaction of propylene with chlorine and water to produce propylene chlorohydrin, which is dehydrochlorinated with lime or caustic soda to yield propylene oxide and a chloride salt.

ARCO Chemicals manufactures propylene oxide using the hydroperoxide process (Kirk and Dempsey, 1982); their plant in Bayport, TX, produces tert-butyl alcohol as a coproduct, while their plant in Channelview, TX, produces α-methylbenzyl alcohol as a coproduct. The hydroperoxide process can be represented by the following reactions:

$$RH + O_2 \rightarrow ROOH$$

$$ROOH + CH_3CH{=}CH_2 \rightarrow CH_3CH\text{-}CH_2 + ROH$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \backslash\ /$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad O$$

When isobutane is used as the RH starting material, tert-butyl alcohol is the coproduct; an ethylbenzene starting material yields the α-methylbenzyl alcohol coproduct.

1.4. USE DATA

The use pattern for propylene oxide is shown in Table 1-3. Nearly all of the propylene oxide produced is used as an intermediate in the synthesis of other chemicals and polymers. It is certified for use as a package fumigant for dried fruits and as a bulk fumigant for foodstuffs such as cocoa,

TABLE 1-3

Use Pattern for Propylene Oxide*

Use	Percent
Urethane polyether polyols	59
Propylene glycol	21
Dipropylene glycol	2
Miscellaneous (glycol ethers, industrial polyglycols, glycerine, surfactants, and isopropanolamines)	9
Export	9
Total	100

*Source: CMR, 1984

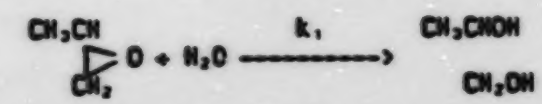
spices, processed nutmeats, starch and gums (Kirk and Dempsey, 1982); it may also be used in mixtures with carbon dioxide. Propylene oxide can be used as a stabilizer for methylene chloride, fuel and heating oils, in treating wood for termite resistance, as an acid scavenger and pH control agent, and as a treatment chemical for removing residual catalysts from crude polyolefins. Propylene oxide-ethylene oxide mixtures are used as fuel-air explosives in munitions (Kirk and Dempsey, 1982).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

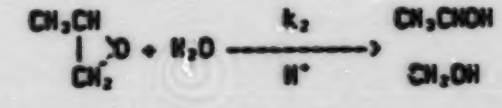
The fate of propylene oxide in the environment depends on the ability of the compound to undergo photochemical, chemical and biological reactions, and to partition from one environmental matrix into another. Data pertinent to the direct or photosensitized photolysis of propylene oxide under environmental conditions were not located in the available literature cited in the Appendix.

2.1. WATER

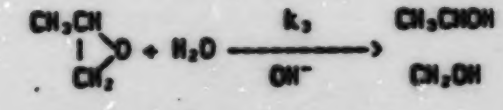
2.1.1. Chemical Degradation/Transformation. Propylene oxide undergoes significant reaction in water by hydrolysis. The chemistry involves the cleavage of a carbon-oxygen bond of the cyclic ether to yield 1,2-propylene glycol (Bogyo et al., 1980). The hydrolysis of propylene oxide (or any epoxide) may be spontaneous (I), acid-mediated (II) or alkali-mediated (III); for propylene oxide (PO), the pathways may be represented as follows:

(I) 

$$\text{Rate} = -dC_{PO}/dt = k_1 C_{PO}$$

(II) 

$$\text{Rate} = -dC_{PO}/dt = k_2 C_{PO} C_{H^+}$$

(III) 

$$\text{Rate} = -dC_{PO}/dt = k_3 C_{PO} C_{OH^-}$$

Table 2-1 summarizes hydrolysis data for propylene oxide. The chemical hydrolysis in the environment is expected to proceed primarily by the spontaneous hydrolysis pathway (Bogyo et al., 1980). At ambient temperature (25°C), the spontaneous rate constants listed in Table 2-1 are 0.69×10^{-6} sec^{-1} and 0.55×10^{-6} sec^{-1}, which produce calculated half-lives of 11.6 and 14.6 days, respectively. Additional hydrolysis rate data has been reported by DeBont et al. (1982); during sterile control runs of a biodegradation study, it was noted that ~10% of the initial propylene oxide was hydrolyzed in 1 day at 30°C in a mineral salt medium.

Epoxides also react with nucleophiles (anions or Lewis bases) by pathways that parallel hydrolysis; however, the chemistry is more complex. The expoxide ring can be cleaved by spontaneous reaction or by acid-catalyzed reaction as shown (Bogyo et al., 1980):

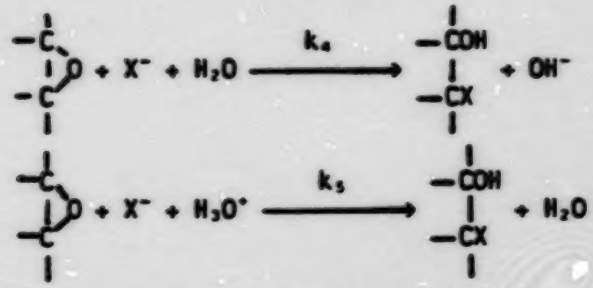


Table 2-2 summarizes specific rate constants for the reactions of propylene oxide with chloride and nitrate ion. Anions can react with the unsymmetrical epoxides (such as propylene oxide) to yield two products (Bogyo et al.,

TABLE 2-1

Hydrolysis Kinetics of Propylene Oxide

Temperature (°C)	Specific Rate Constant[a]		
	$10^a k_1$ sec-1	$10^a k_2$ ℓ/mol-sec	$10^a k_3$ ℓ/mol-sec
1.0	NA	2.79[b]	NA
10.1	NA	8.46[b]	NA
25	0.69[c]; 0.55[f]	NA	0.87[e]
30	NA	74.5[b]	NA
37	2.22[d]	124[d]	2.75[d]
40	NA	199[b]	NA
60	21.1[c]	NA	NA

[a] k_1, k_2 and k_3 are described in the text.

[b] Long et al., 1957

[c] Koskikallio and Whalley, 1959

[d] Ross, 1950

[e] Pritchard and Siddiqui, 1972

[f] Mabey and Mill, 1978

NA = Not available

TABLE 2-2

Rate Constants for the Reaction of Propylene Oxide with Chloride and Nitrate Ion

Lewis Base or Anion	Temperature (°C)	$10^3 k_4$ (ℓ/mol-sec)[a]	$10^2 k_5$ ($ℓ^2/mol^2$-sec)[a]
Cl^-	0	517 (THF)[d]	NA
	20.0	0.259 (9:1 water-dioxane)[c]	10.64 (9:1 water-dioxane)[c]
	30.1	0.728 (9:1 water-dioxane)[c]	30.1 (9:1 water-dioxane)[c]
	40.0	2.14 (9:1 water-dioxane)[c]	81.5 (9:1 water-dioxane)[c]
	27	NA	21.17[b]
NO_3^-	20.0	NA	0.410 (water)[e]

[a] k_4 and k_5 are described in the text.

[b] Ross, 1950

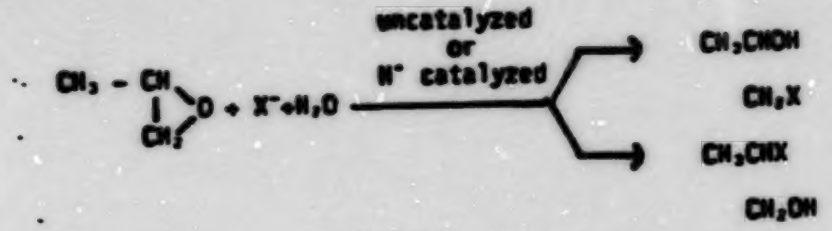
[c] Addy and Parker, 1963

[d] Addy and Parker, 1965

[e] Petty and Nichols, 1954

NA = Not available

1980). The products resulting from anion attack at the primary carbon atom or at the secondary carbon atom of propylene oxide are as follows:



Salient information on the product distribution for propylene oxide reaction with chloride is summarized in Table 2-3. Reaction at neutral (or alkaline) pH yields mainly the secondary alcohol with production of the primary alcohol increasing as the pH is lowered. Using the rate constants in Table 2-2, the half-life of propylene oxide in water by chloride reaction can be calculated at pH 7 and 20°C by assuming the chloride concentration of freshwater to be ~5×10^{-4} M (Smart and Nancy, 1984) and 0.53 M in seawater; the half-life in freshwater is ~6200 days, while in seawater the half-life is ~5.8 days.

The combined half-life data for hydrolysis in the pH range of 5-9 and chloride ion reaction can now be estimated. The following rate constants at 25°C were either taken directly from Tables 2-1 and 2-2 or from Bogyo et al. (1980):

$k_1 = 0.62\times10^{-6}$ sec^{-1}

$k_2 = 52\times10^{-3}$ $L/mol\text{-}sec$

$k_3 = 0.87\times10^{-4}$ $L/mol\text{-}sec$

$k_4 = 0.52\times10^{-3}$ $L/mol\text{-}sec$

$k_5 = 20\times10^{-2}$ $L^2/mol^2\text{-}sec$

TABLE 2-3

Product Distribution from Unsymmetrical Epoxide Reaction with Chloride [a,b]

Epoxide	Temperature (°C)	pH	Percentage Product	
			$RCHOHCH_2X$	$RCHXCH_2OH$
Propylene oxide	20.0	7.0	91	9
		4.5	75	25
		3.8	68	32
		3.6	66	34
	30.1	7.0	88	12
		4.5	73	27
		3.8	66	34
		3.6	65	35
	40.0	7.0	86	14
		4.5	72	28
		3.8	64	36
		3.6	64	36

[a]Source: Addy and Parker, 1963, 1965

[b]In 9:1 (v/v) water dioxane

The half-lives calculated (Table 2-4) results from the above rates by utilizing the equation, $t_{1/2}=0.693/k_T$ (where $k_T=k_H[H^+]/+k_o+k_{OH}[OH^-]$). As can be noted from Tables 2-1 and 2-2, the rates are dependent on temperature; therefore, at colder ambient temperatures, the degradation of propylene oxide will require longer periods of time. The combined half-lives in Table 2-4 do not include microbial degradation. In addition, the rate constants for the chloride reactions were determined in 9:1 water:dioxane solutions, which might possibly accelerate the reaction in comparison with pure water. Conway et al. (1983) determined in laboratory experiments that the half-life of ethylene oxide in a 3% NaCl solution (~0.53 M chloride) is ~30% shorter than the half-life in pure water; whereas, Bogyo et al. (1980) predicted that the half-life of ethylene oxide in a 3% NaCl solution would be ~3 times shorter than the half-life in pure water by using the same prediction methods used to make the calculations for propylene oxide in Table 2-4. Therefore, the degradation of propylene oxide in seawater may not be as rapid as calculated in Table 2-4, but will probably be significantly more rapid than in freshwater.

Anbar and Neta (1967) reported that the rate constant for the reaction of OH radicals and propylene oxide in water is 1.4×10^8 L/mol-sec. Assuming an OH radical concentration of 10^{-17} M in natural water, a half-life of 15.7 years can be calculated, which has no environmental significance. Smart and Nancy (1984) reported that nitrate is usually present in surface waters in only trace amounts, but may occur in high concentrations in groundwater. The nitrate rate constant reported in Table 2-2 suggests that this reaction is not environmentally significant except in highly uncommon conditions of acidic water and high NO_3^- levels.

TABLE 2-4

Calculated Aqueous Half-Lives ($t_{1/2}$) in Days of Propylene Oxide at 25°C

Reaction	Half-Life (days)		
	pH 5	pH 7	pH 9
Hydrolysis	7.0	12.9	12.9
Chloride			
Freshwater	3085	3085	NR
Seawater	2.1	2.1	NR
Combined half-lives (for hydrolysis plus chloride reaction)			
Freshwater	7.0	12.9	NR
Seawater	1.6	2.4	NR

NR = Not reported

2.1.2. Microbial Degradation. DeBont et al. (1982) reported that a bacterium designated Nocardia A60 is capable of using propylene oxide aerobically as a sole carbon and energy source for growth. In a batch culture with a mineral salt solution at 30°C, N. A60 grew on propylene oxide (1 g/ℓ) with the culture doubling in 6.4 hours. In respiration studies with whole cells, the rate of oxygen uptake by the bacterium was 0.05 μmol O_2 consumed/min/mg protein. The initial step in the metabolism of propylene oxide by N. A60 was an epoxidase-catalyzed hydrolysis that yielded 1,2-propanediol.

Hou et al. (1979) isolated various methane-utilizing microorganisms from lake water and soil samples from New Jersey and examined their ability to oxidize C_2 to C_4 n-alkenes to their corresponding 1,2-epoxides. Propylene was found to be oxidized to propylene oxide by a variety of species of methylotrophic bacteria including Methylosinus, Methylocystis, Methylomonas, Methylobacter, Methylococcus and Methylobacterium. Enzymatic cell suspensions from these methylotrophic bacteria, however, were not able to biodegrade propylene oxide during a 6-hour incubation period and only slightly degraded propylene oxide, yielding propylene glycol, during a 24-hour incubation period.

Bridie et al. (1979a) measured the BOD of a number of petrochemicals using a 5-day BOD test; for propylene oxide, a BODT of 8% was measured using a filtered effluent from a biological sanitary waste treatment plant, while a BODT of 9% was measured using an adapted seed. Hatfield (1957) found that the BOD of propylene oxide was small compared with the BODT. Gorban and Petrenko (1972) reported that Pseudomonas graveoleus and P. fluorescens are capable of biodegrading propylene oxide (<700 ppm) in industry wastewaters by using aeration tanks.

There are no data available that indicate that propylene oxide is readily degradable by microorganisms in the natural environment. The data above may suggest that propylene oxide can be slowly biodegraded with appropriately acclimated microbes. Thom and Agg (1975) listed propylene oxide as a compound that should be degradable by biological sewage treatment provided suitable acclimatization can be achieved.

2.1.3. Transport. The transport of propylene oxide in the aquatic environment depends on the ability of the compound to volatilize, to adsorb to particulate organic matter and sediment and to bioaccumulate in aquatic organisms. Although experimental studies are not available, adsorption and bioaccumulation are not likely to be environmentally significant. The extremely high WS of propylene oxide (405,000 ppm at 20°C) suggests that significant partitioning from water into sediment will not occur. The high WS and low K_{OW} (0.03) predict that bioaccumulation is not significant. A BCF can be estimated from the WS or K_{OW} by using the following equations:

$$\text{Log BCF} = 2.791 - 0.564 \log \text{WS (in ppm)} \quad \text{(Kenaga and Goring, 1980)} \quad (2\text{-}1)$$

$$\text{Log BCF} = 0.76 \log K_{OW} - 0.23 \quad \text{(Veith et al., 1980)} \quad (2\text{-}2)$$

The BCFs for equations 2-1 and 2-2 are calculated to be 0.4 and 0.6, respectively.

Experimental data pertaining to the measurement of the volatility rate of propylene oxide from water were not located in the available literature cited in the Appendix. The K_H of a compound at equilibrium (which is the reciprocal of the unitless Henry's Law constant) can be estimated by the

following equation in which WS is in ppm, T is in °K, VP is in mm Hg and MW is in g/mol (Swann et al., 1983):

$$K_H = \frac{(0.0624)\ (WS)\ (T)}{(VP)\ (MW)}$$

For propylene oxide at 20°C, the K_H is calculated to be 290. With units, Henry's Law constant can be calculated to be 8.3×10^{-5} atm-m³/mol; this value suggests that volatilization of propylene oxide from water is likely to be significant (Lyman et al., 1982). The U.S. EPA's EXAMS Computer Simulation (Burns et al., 1981) can be used to predict propylene oxide volatilization half-lives from water. Based on the WS and VP at 20°C, the half-lives range from 3 days in river water to 18 days in an oligotrophic lake. This suggests that volatilization of propylene oxide is competitive with its chemical degradation in water.

2.2. AIR

The atmospheric chemical removal processes include reactions with hydroxyl or other radicals, reaction with ozone and photolytic transformations. Using a modified smog chamber method, the rate constant for the reaction of OH radicals with propylene oxide at 27°C has been determined to be 1.3×10^{-12} cm³/molecule-sec (Atkinson et al., 1979). Cupitt (1980) used this rate constant to calculate an atmospheric residence time of 8.9 days, with the anticipated products being $CH_3C(O)OCHO$, $CH_3C(O)CHO$, H_2CO and $HC(O)OCHO$. The 1.3×10^{-12} cm³/molecule-sec rate constant can also be used to calculate a half-life of 6.2 days, assuming an atmospheric OH radical concentration of 10^6 molecules/cm³. Pertinent data regarding environmental photolysis or reaction with ozone or radicals other than hydroxyl radicals were not located in the available literature cited in the Appendix.

The physical removal processes include dissolution, adsorption on aerosol particles and dry deposition. The latter two mechanisms can be reasonably predicted to have no significance. Because of the high WS of propylene oxide, dissolution may be possible. Entrapment in clouds and raindrops may occur with subsequent removal by rainfall. Cupitt (1980) suggested that the atmospheric physical removal probability of propylene oxide is unlikely because the calculated dissolution half-life is >0.5 year. This estimated half-life, however, is not applicable to short-term localized conditions under which propylene oxide is most likely to be removed from the environment.

2.3. SOIL

Pertinent data regarding the fate and transport of propylene oxide in soil are limited. The microbial degradation data from Section 2.1.2. suggests that propylene oxide may be biodegradable by properly acclimated microorganisms. The significance of this to the transport of propylene oxide in soil is uncertain because appropriate soil degradation studies are not available. The aqueous hydrolysis of propylene oxide has been shown to be significant (see Section 2.1.1.); therefore, chemical hydrolysis in moist soils may be possible.

The high WS of propylene oxide suggests that it may be easily leached in soil. K_{oc} values may be estimated by using the following regression equations developed by Kenaga and Goring (1978):

$$(1)\ \text{Log } K_{oc} = 3.64 - 0.55 \log WS \qquad (2\text{-}3)$$

$$(2)\ \text{Log } K_{oc} = 0.544\ K_{ow} + 1.377 \qquad (2\text{-}4)$$

K_{oc} for equations 2-3 and 2-4 are calculated to be 3.6 and 24.7, respectively, indicating the propylene oxide is highly mobile in soil. In addition, a recent soil sorption prediction method based on molecular topology and quantitative structure-activity relationships (Sabljic, 1984), which may have more prediction accuracy than the use of WS and K_{ow}, predicts a K_{oc} of 30 for propylene oxide (indicating the same results as before).

The high relative VP of propylene oxide suggests that it may evaporate rapidly from dry soil surfaces. The volatility rate from wet soil is directly proportional to the VP and inversely proportional to the WS multiplied by the K_{oc} (Swann et al., 1983). Without experimental data, it is difficult to assess the relative importance of propylene oxide volatilization from wet soils; however, some evaporation is likely to occur.

2.4. SUMMARY

Propylene oxide will not persist in the environment because of its chemical reactivity. In water, propylene oxide undergoes significant hydrolysis with a half-life at 25°C of ~13 days. Degradation in water is accelerated by the presence of chloride indicating that chemical removal in seawater will be significantly more rapid than in freshwater. The data suggest that propylene oxide may be biodegraded by properly acclimated microorganisms. Partitioning of propylene oxide from water into sediment and its bioaccumulation in aquatic organisms are not likely to be significant; however, the volatilization of propylene oxide from water into the atmosphere appears to be significant.

In the ambient atmosphere, propylene oxide reacts relatively rapidly with hydroxyl radicals to produce a calculated atmospheric residence time at 27°C of 8.9 days (Cupitt, 1980). Pertinent data regarding the reaction of

propylene oxide with other radicals, ozone or UV radiation were not located in the available literature cited in the Appendix. Propylene oxide may be removed from air by rainfall because of to its high WS.

In soil, propylene oxide is likely to undergo significant leaching in wet conditions; wet conditions may also subject propylene oxide to potential hydrolysis. Propylene oxide is likely to evaporate rapidly from dry soil surfaces.

3. EXPOSURE

3.1. WATER

The U.S. EPA STORET Data Base contains one observation for propylene oxide. This observation was made at a water effluent from Olin Corporation's Brandenburg, KY, chemical production facility on February 2, 1974. During 1974, Olin Corporation was manufacturing propylene oxide in Brandenburg, KY; the concentration of propylene oxide in the effluent was reported to be 0.047 mg/L. Other monitoring data for propylene oxide in water were not located in the available literature cited in the Appendix.

3.2. FOOD

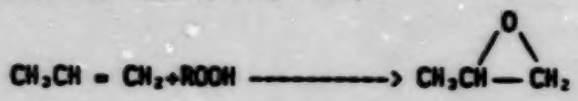
Pertinent data regarding the monitoring of propylene oxide in ready-to-eat foods were not located in the available literature cited in the Appendix. IARC (1976) reported several studies made to determine the persistence of propylene oxide in foods fumigated with the compound. In one study, levels of 4000-9000 mg/kg propylene oxide were found in samples of linseed, soybean, sesame, rapeseed, olive and castor oils, lard, beef tallow, butter, mayonaise and shortening, and in linoleic and oleic acids after fumigation at 50°C for 2 hours; after storage for 24 hours at 37°C, no propylene oxide was found in linseed, soybean and olive oils, but 4147 mg/kg were found in lard and 5910 mg/kg were found in oleic acid.

3.3. INHALATION

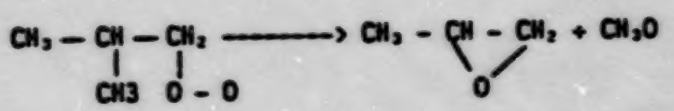
Pertinent data regarding the monitoring of propylene oxide in ambient air other than in the workplace were not located in the available literature cited in the Appendix. Although no monitoring data is available, Bogyo et al. (1980) suggested that propylene oxide may be emitted to the atmosphere from automobile exhaust and from combustion exhausts of stationary sources that burn hydrocarbons. Hughes et al. (1959) used gas-liquid partition

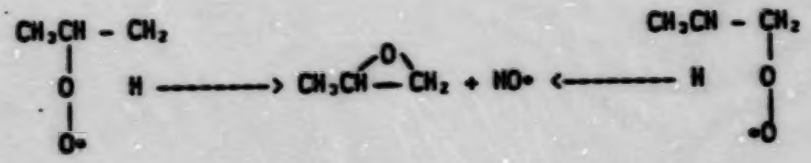
chromatography to separate and identify oxygenated derivatives of hydrocarbons in the combustion products of hydrocarbon fuels; propylene oxide was among the oxygenated combustion products identified. Barnard and Lee (1972) identified propylene oxide in the oxygenated combustion products from n-pentane combustion.

- The epoxides can be formed in the photochemical smog cycle. Olefins can be converted to the corresponding epoxide by reaction with an organic peroxide (Altshuller and Buffalini, 1965):



Alkyl peroxides can decompose to yield an epoxide and oxy radical (NAS, 1976):





3.4. DERMAL

Pertinent data regarding the dermal monitoring of propylene oxide for dermal exposure were not located in the available literature cited in the Appendix.

4. PHARMACOKINETICS

Pertinent data regarding the pharmacokinetics of propylene oxide were not located in the available literature cited in the Appendix. Based on toxicity data, absorption can occur by all natural routes of exposure (Section 5.6.). Because of to the high WS of propylene oxide, absorption from the lungs and gastrointestinal tract is likely to occur fairly efficiently and rapidly; however, bioaccumulation is not likely to occur (Bogyo et al., 1980). Based on the rapid rate of epoxide metabolism to diols by expoxide hydrolase, metabolism of propylene oxide is expected to proceed rapidly. Ehrenberg and Hussain (1981) estimated that the half-life for hydrolysis of propylene oxide in conditions of the stomach (pH 1 and 37°C) is ~1 minute.

5. EFFECTS

5.1. CARCINOGENICITY

The carcinogenicity of propylene oxide has been tested in groups of 50 female Sprague-Dawley rats treated by gavage at two dose levels for up to 150 weeks (Dunkelberg, 1982). Rats were given propylene oxide at 0, 15 and 60 mg/kg bw in salad oil twice weekly for their lifetime or 150 weeks (a total of 219 treatment days and average total doses of 0, 2714 and 19,798 mg/kg). Both vehicle-treated, control and untreated control groups were included for comparison. Because of to the volatility of propylene oxide, treatment solutions were prepared immediately before use. A thorough necropsy with histopathological examination of major organs and stomach and duodenum was performed on all available rats. Survival of rats treated with propylene oxide and control groups was comparable. Rats treated with propylene oxide developed stomach tumors, primarily squamous-cell carcinomas, the first appearing during the 79th week of treatment. The incidences of squamous-cell carcinoma of the forestomach were 19/50 and 2/50 among high- and low-dose rats given propylene oxide, while no stomach tumors were observed in the oil-treated or untreated controls (0/100 combined) (Table 5-1). Numerous mammary tumors and low numbers of randomly-occurring tumors were reported among all experimental groups and were not regarded as being treatment-related.

A carcinogenesis bioassay of propylene oxide in F344 rats and B6C3F1 mice has been completed by the National Toxicology Program (NTP, 1985). Propylene oxide was administered by inhalation at 0, 200 or 400 ppm (475 or 950 mg/m^3) for 6 hours/day, 5 days/week for 103 weeks. Groups of 50 animals of each sex and species were exposed at each concentration.

TABLE 5-1

Tumor Incidence in Sprague-Dawley Rats*

Exposure Route	Sex	Concentration (mg/kg)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound (%)	Vehicle	Target Organ	Tumor Type	Tumor Incidence
Oral	F	60 mg/kg 2 times/week (10,798 mg/kg total dose)	147 (219 treatments)	150	99.7%	salad oil	forestomach	squamous-cell carcinoma	19/50
Oral	F	15 mg/kg 2 times/week (2714 mg/kg total dose)	147 (219 treatments)	150	99.7%	salad oil	forestomach	squamous-cell carcinoma	2/50
Oral	F	0.0 mg/kg	147 (219 treatments)	150	NA	oil only	forestomach	squamous-cell carcinoma	0/50
NA	F	0.0 mg/kg	NA	150	NA	untreated	forestomach	squamous-cell carcinoma	0/50

QUALITY OF EVIDENCE

Strengths of Study: The study was conducted for a long period of time. Treatment was given by a relevant route of administration. Two dose levels and vehicle and untreated control groups were maintained. Thorough necropsy was performed.

Weakness of Study: Only female rats were tested. No statistical analyses were performed.

Overall Adequacy: Adequate

Comments: Average total doses of 10,798 and 2714 mg/kg during the entire study were administered at the high and low dose levels, respectively.

*Source: Dunkelberg, 1982

NA = Not applicable

Survival of exposed rats was comparable with that of controls, while survival in mice was decreased in a dose-related manner, but significantly only in high-dose males and females. Terminal body weights of high-dose male and female rats and mice were 6-22% lower than controls.

The primary tissue affected by inhalation of propylene oxide in rats and mice was the respiratory epithelium of the nasal turbinates. Suppurative inflammation, epithelial hyperplasia and squamous metaplasia occurred in male and female rats in a dose-related manner. Papillary adenoma of the nasal turbinate epithelium and underlying submucosal gland was observed in three female and two male rats exposed to 400 ppm propylene oxide. No similar tumors were observed among low dose or control rats (Table 5-2). Based on the thorough necropsy and histopathological examination of major tissues and organs, no other cytopathologies or tumor responses among male or female rats were considered treatment-related. There was an increase in the incidence of C-cell adenomas and carcinomas of the thyroid and endometrial sarcomas and polyps among treated female rats, but the NTP (1985) regarded these as not treatment-related, because of high incidences of endometrial tumors among historic controls and a lack of evidence that the thyroid is a target organ of propylene oxide.

In mice, the nasal epithelium was affected by inhalation of propylene oxide with inflammation occurring in a dose-related manner among males and females. In addition to the nonneoplastic changes, a squamous-cell carcinoma and a papilloma were observed among high-dose male mice, and two high-dose female mice had nasal adenocarcinomas. The vascular endothelium within the nasal epithelium was also affected, with a high incidence of hemangiomas and hemangiosarcomas among high-dose males and female mice. The combined incidence of these tumor types was 10/50 and 5/50 among high-dose

TABLE 5-2

Animal Tumor Incidence by the Inhalation Route*

Species/ Strain	Sex	Concentration (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound (%)	Vehicle	Target Organ	Tumor Type	Tumor Incidence (p value)
Rat/F344	M	400 6 hours/day, 5 days/week	103 (491 exposures)	103	>99.9%	air/vapor	nasal epithelium	papillary adenoma	2/50
Rat/F344	M	200 6 hours/day, 5 days/week	103 (491 exposures)	103	>99.9%	air/vapor	nasal epithelium	papillary adenoma	0/50
Rat/F344	M	0.0	103 (491 exposures)	103	NA	air only	nasal epithelium	papillary adenoma	0/50
Rat/F344	F	400 6 hours/day, 5 days/week	103 (491 exposures)	103	>99.9%	air/vapor	nasal epithelium	papillary adenoma	3/50 (p=0.10)
Rat/F344	F	200 6 hours/day, 5 days/week	103 (491 exposures)	103	>99.9%	air/vapor	nasal epithelium	papillary adenoma	0/50
Rat/F344	F	0.0	103 (491 exposures)	103	NA	air only	nasal epithelium	papillary adenoma	0/50
Mice/B6C3F1	M	400 6 hours/day, 5 days/week	103 (491 exposures)	103	>99.9%	air/vapor	nasal cavity	hemangioma/ hemangiosarcoma	10/50 (p=0.001)
Mice/B6C3F1	M	200 6 hours/day, 5 days/week	103 (495 exposures)	103	>99.9%	air/vapor	nasal cavity	hemangioma/ hemangiosarcoma	0/50
Mice/B6C3F1	M	0.0	103 (491 exposures)	103	NA	air only	nasal cavity	hemangioma/ hemangiosarcoma	0/50
Mice/B6C3F1	F	400 6 hours/day, 5 days/week	103 (491 exposures)	103	>99.9%	air/vapor	nasal cavity	hemangioma/ hemangiosarcoma	5/50 (p=0.028)
Mice/B6C3F1	F	200 6 hours/day, 5 days/week	103 (495 exposures)	103	>99.9%	air/vapor	nasal cavity	hemangioma/ hemangiosarcoma	0/50

TABLE 5-2 (cont.)

Species/ Strain	Sex	Concentration (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound (%)	Vehicle	Target Organ	Tumor Type	Tumor Incidence (p value)
Mice/B6C3F1	F	0.0	103 (495 exposures)	103	NA	air only	nasal cavity	hemangioma/ hemangiosarcoma	0/50

QUALITY OF EVIDENCE

Strengths of Study: Prolylene oxide was administered by a relevant route to male and female rats and mice for 2 years. Complete necropsy and histopathological examination of all available animals were performed. Statistical analyses were performed.

Weakness of Study: The high dose level in rats may not have been near the MTD.

Overall Adequacy: Adequate

Comments: The NTP (1985) regarded data in rats as providing "some evidence of carcinogenicity"; in mice, "clear evidence of carcinogenicity" was indicated.

*Source: NTP, 1985

NA = Not applicable

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males and females, respectively, with no tumors of this type occurring among low-dose or control mice of either sex (see Table 5-2). Under the conditions of this bioassay, the NTP (1985) concluded that there was "some evidence of carcinogenicity" for male and female F344 rats (based on nasal papillary adenoma incidence) and "clear evidence of carcinogenicity" in male and female B6C3F1 mice (increased incidence of hemangiomas and hemangiosarcomas of the nasal turbinates).

A 28-month inhalation bioassay of propylene oxide was conducted by the Dow Chemical Company (Reuzel and Kuper, 1983) in Cpb:Wu Wistar rats. Groups of 100 animals of each sex were exposed at 0, 30, 100 or 300 ppm (0, 71, 238 or 713 mg/m^3) propylene oxide for 6 hours/day, on 5 days/week for 123 (females) or 124 (males) weeks. Interim kills of 10 animals of each sex and dose group were made at 12, 18 and 24 months of exposure. Slight weight reduction and increased mortality occurred among male and female rats exposed at 300 ppm compared with controls. Effects of propylene oxide inhalation were found in the nasal cavity of high-dose rats and included hyperplasia of the respiratory epithelium (47/128 combined males and females) and degeneration of the olfactory epithelium (57/128). Nasal and respiratory tract tumors among high-dose animals included one nasal squamous-cell carcinoma, one tracheal squamous-cell carcinoma, and one each of squamous-cell carcinoma and adenocarcinoma of the laryngopharynx. There were no similar tumors among control group rats (0/70) or low-dose animals. Since the incidence of each tumor type was only 1 of 70 (all tumors occurring in different rats), the increase is not significant, but taken together, a carcinogenic response is suggested. The incidence of mammary tumors among female rats (both tumor-bearing animals and tumors/rat) showed a dose-related increase, with 3, 6, 5 and 8 carcinomas occurring among the

males and females, respectively, with no tumors of this type occurring among low-dose or control mice of either sex (see Table 5-2). Under the conditions of this bioassay, the NTP (1985) concluded that there was "some evidence of carcinogenicity" for male and female F344 rats (based on nasal papillary adenoma incidence) and "clear evidence of carcinogenicity" in male and female B6C3F1 mice (increased incidence of hemangiomas and hemangiosarcomas of the nasal turbinates).

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females exposed at 0, 30, 100 and 300 ppm, respectively. Benign mammary tumors occurred in 32, 30, 39 and 47 females of the respective dose groups. The average number of tumors/tumor-bearing rat was 1.3, 2.1, 2.2 and 2.4, respectively.

The carcinogenicity of propylene oxide following subcutaneous injection was tested in female NMRI mice (Dunkelberg, 1979, 1981). Groups of 100 animals were treated on a weekly basis with 2.5, 1.0, 0.3 and 0.1 mg propylene oxide/animal. Vehicle (tricaprylin) and untreated controls were also maintained. Propylene oxide was administered for 95 weeks with average total doses of 165.4, 72.8, 21.7 and 6.8 mg/mouse. Injection-site sarcomas showed a dose-related increase with ~2-16% of the treated mice affected, while none (0/83) occurred among vehicle controls or untreated controls (0/90).

In an early subcutaneous injection study, Walpole (1958) reported that 8 of 12 rats developed injection site tumors after receiving 1500 mg propylene oxide/kg total dose (in arachis oil) over a 325-day period. Tumors developed during the latency period (after treatment was terminated), were observed between days 507 and 739 of the study. In a parallel study in which 12 rats were given a total dose of 1500 mg/kg dissolved in water, only two injection site sarcomas occurred (on days 158 and 737). Additional details on the protocol of the study or data on control group rats were not available.

5.2. MUTAGENICITY

Several reviews of the mutagenicity data for propylene oxide are available (IARC, 1976; Bogyo et al., 1980; Cavender, 1983). Helmes et al. (1982) classified propylene oxide as a positive mutagen based on the available data from Ames' assays. A summary of recent mutagenicity data on propylene oxide (Table 5-3) clearly indicates that base-pair mutagenesis occurs in strains

TABLE 5-3

Summary of Mutagenicity Data for Propylene Oxide

Assay	Indicator/ Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium	99%	plate incorporation	NS	-S-9	+	Positive in TA100, TA1535 negative in TA98, TA1537	Ude et al., 1978
	S. typhimurium	99.5%	spot test	10 µL/plate	±S-9	+	Positive in TA100, TA1535 with or without metabolic activation Negative in TA1537, TA1538, TA98	Bootman et al., 1979
	S. typhimurium	99.5%	plate incorporation	100-700 µg/plate	-S-9	+	Positive in TA1535, TA100	Bootman et al., 1979
	S. typhimurium	NS	plate application	2.5-20 µL/plate	-S-9	+	Base pair mutagen; positive in TA1535, TA100	McMahon et al., 1979
	S. typhimurium	99%	plate incorporation	10-200 µL/plate	-S-9	+	Positive in TA1535, TA100 Negative in TA98, TA1537	Pfeiffer and Dunkelberg, 1980
	S. typhimurium	NS	plate incorporation	400 µL/plate	-S-9	+	Positive in TA100	Yamaguchi, 1982
	S. typhimurium	NS	plate incorporation	350 µL/plate	+	+	Positive in TA100; mutagenic activity decreased by S-9	Yamaguchi and Nakagawa, 1983
	Escherichia coli	99.5%	spot test	10 µL/plate	±S-9	+	Positive in WP2, CM871, CM891	Bootman et al., 1979
	E. coli	technical grade	liquid media	20-10,000 µM	-S-9	+	WP2uvrA	Heminki et al., 1980
	E. coli	NS	plate incorporation	2.5-20 µL/plate	-S-9	+	Positive in WP2, WP2uvrA-	McMahon et al., 1979
	Klebsiella pneumoniae	analytical grade	liquid medium	0.5, 1.0 µM	-S-9	+	Propylene oxide more mutagenic than longer alkyl chain epoxides	Voogd et al., 1981
Forward mutation	Schizosaccharo-myces pombe	purest available	liquid medium	3-30 mM	±S-9	+	Strain P1; S-9 did not greatly affect mutagenic action	Migliore et al., 1982
Recessive lethal mutation	Drosophila melanogaster	98%	vapor exposure	24 hours at 645 ppm	NA	+	Increase in sex-linked recessive mutations in mature sperm and spermatocyte stages	Hardin et al., 1983a

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TABLE 5-3 (cont.)

Assay	Indicator/ Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Forward mutation	Chinese hamster ovary cells HGPRT	NS	vapor exposure	8-40 µg/cm³	none	+	Mutations increased at toxic levels	Zamora et al., 1983
Chromosome aberrations	rat hepatocyte	NS	liquid medium	25-100 µg/ml	none	+	Greatest effect on chromatid gap frequency	Dean and Hodson-Walker, 1979
DNA strand breaks	rat hepatocyte	NS	liquid medium	0.03-3.0 mM	none	+	Significant increase in DNA single-stranded breaks	Sina et al., 1983
Chromosome aberrations	human lympho-cytes	99.5%	liquid medium	1.85, 9.25 µg/ml	none	+	Significant ($p<0.01$) increase in aberrations (chromatid gaps, breaks; chromosome gaps, breaks, fragments)	Bootman et al., 1979
Micronuclei test	mouse bone marrow cells	99.5%	oral, gavage	2 doses at 100, 250 or 500 mg/kg	NA	-	No increase in micronucleated cells	Bootman et al., 1979
		99.5%	i.p.	2 doses at 75, 150 or 30 mg/kg	NA	+	Increased micronucleated cells at 300 mg/kg dose level, $p<0.001$	Bootman et al., 1979
Dominant lethal mutation	mouse	99.5%	oral, gavage	14 doses at 50 or 250 mg/kg	NA	-	No clear increase in number of implants or implant deaths (early or late)	Bootman et al., 1979
Spermhead morphology	mouse	98%	inhalation	300 ppm, 7 hours/day for 5 days	NA	-	No increase in abnormal sperm determined at 1, 3, 5, 7 or 9 weeks after exposure	Hardin et al., 1983a
Dominant lethal mutation	rat	98%	inhalation	300 ppm, 7 hours/day for 5 days	NA	-	Only females mated during week 1 after exposure had an increased % of preimplantational losses	Hardin et al., 1983a
Chromosome aberrations	human lymphocytes	NS	occupational exposure	NS	NA	ND	Exposure was primarily to ethylene oxide and many other compounds; increased chromosome aberrations in workers exposed ≥20 years	Thiess et al., 1981
DNA synthesis and repair	human lymphocytes	NS	occupational exposure	<12 ppm 2-20 years	NA	+	Ability of lymphocytes to synthesize and repair DNA among propylene oxide-exposed workers was reduced ($p<0.001$)	Pero et al., 1982

NA = Not applicable; ND = not determined; NS = not stated; i.p. = intraperitoneal

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TA100 and TA1535 of Salmonella typhimurium. In addition to the positive reversion mutation in S. typhimurium (from histidine dependence), reverse mutation in Escherichia coli (from tryptophan dependence) has also been demonstrated (Bootman et al., 1979; Hemminki et al., 1980; McMahon et al., 1979).

Propylene oxide has been shown to be a positive mutagen in assays in yeast (Migliore et al., 1982), Drosophila melanogaster (Hardin et al., 1983a) and a number of in vitro mammalian cell assays (see Table 5-3). Vapor exposure of propylene oxide caused increased lethal mutations in D. melanogaster, with spermatocytes and mature sperm apparently being sensitive stages (Hardin et al., 1983a). In mammalian cells (rat hepatocytes and human lymphocytes) exposed in vitro, chromatid gaps, single-strand DNA breaks and chromosomal gaps, breaks and fragments were increased following propylene oxide exposure.

Evidence for the mutagenicity of propylene oxide following in vivo exposure is not conclusive. Bootman et al. (1979) exposed mice to propylene oxide by gavage and intraperitoneal injection, and reported no increase in the frequency of micronucleated polychromatic erythrocytes following ingestion; however, a positive result occurred following intraperitoneal injection. No mutagenic activity was indicated in rat or mouse dominant lethal assays (Hardin et al., 1983a; Bootman et al., 1979) or mouse spermhead morphology examinations (Hardin et al., 1983a) following in vivo inhalation or ingestion of propylene oxide (see Table 5-3). In human workers exposed occupationally to propylene oxide and to many other epoxides and industrial chemicals for $\geq$20 years, an increase in lymphocyte chromosomal aberrations was indicated (Thiess et al., 1981); however, propylene oxide could not be

implicated as the causative agent. Pero et al. (1982) found that lymphocytes from a group of workers exposed primarily to propylene oxide at levels <12 ppm for 2-20 years had a decreased DNA repair and synthesis proficiency. The mechanism by which propylene oxide retarded unscheduled DNA synthesis in lymphocytes of workers was not discussed.

The mechanism of mutagenic action of propylene oxide has been discussed recently by numerous researchers (Walles and Solveig, 1974; Hemminki, 1979; Hemminki and Falck, 1979; Agarwal et al., 1979; Hemminki et al., 1980; Phillips et al., 1980; Garro and Phillips, 1980; Randerath et al., 1981; Djuric, 1984). Direct alkylation of isolated DNA or 4-(p-nitrobenzyl)pyridine and deoxyguanosine by propylene oxide has been demonstrated in most of these studies. Single-stranded DNA was alkylated much more rapidly than double-stranded DNA. The alkylation rates of propylene oxide and other epoxide compounds correlated well with their mutagenic potency (Hemminki and Falck, 1979). Primarily, N-alkylation occurs with the order of deoxynucleoside reactivity being deoxyguanosine>deoxyadenosine>thymidine>deoxycytidine in DNA exposed to propylene oxide (Djuric, 1984).

5.3. TERATOGENICITY

The National Institute for Occupational Safety and Health (NIOSH) commissioned a teratogenicity study of propylene oxide in rats and rabbits (Hackett et al., 1982; Hardin et al., 1983b). Propylene oxide was administered by inhalation at 500 ppm (1188 mg/m³) for 7 hours/day. Groups of 50 female Sprague-Dawley rats were exposed to filtered air (group 1), propylene oxide on days 7-16 of gestation (group 2), propylene oxide on days 1-16 of gestation (group 3), or propylene oxide for 3 weeks (5 days/week) before mating and daily on days 1-16 of gestation (group 4). Rabbits (30 New Zealand does/group) were exposed to filtered air (group 1), propylene oxide

on days 7-19 of gestation (group 2) and propylene oxide on days 1-19 of gestation (group 3). Necropsies and examination of uteri were performed on rats sacrificed at 21 days of gestation and rabbits at day 30 of gestation.

In rats, food consumption was decreased slightly among females exposed to propylene oxide, while body weight of dams was insignificantly decreased following conception. Changes in relative organ weights of exposed dams compared with controls may have been due to toxic effects or decreased body weights. Pulmonary inflammation was evident following propylene oxide inhalation. Exposure to propylene oxide before mating had no apparent effect on mating performance but did affect reproductive capacity. Dams that were exposed before mating (group 4) had fewer corpora lutea, implantation sites and live fetuses compared with controls. The number of resorptions among dams exposed during gestation was increased, with those exposed on days 7-16 having the highest number. Fetotoxicity was evident, with reduced fetal size and weight and reduced ossification (ribs and vertebrae) among rats exposed to propylene oxide in utero. The frequency of wavy ribs was increased in all groups of fetuses exposed to propylene oxide. Major malformations that were due to propylene oxide exposure were not demonstrated.

Hackett et al. (1982) reported that food consumption among rabbits exposed to propylene oxide was decreased while body weights were not significantly different from those of nonexposed rabbits. Other toxic effects of propylene oxide inhalation on exposed rabbits were not reported. Although only 11 of 30 inseminated rabbits exposed on days 7-19 were pregnant, the cause was not considered to be exposure-related since pregnancy rates among other groups (17/30 controls; 19/30 exposed on days 1-19) were low. Parameters of reproductive performance (number of corpora lutea, implantation sites and live and dead fetuses) were similar for all groups. Fetal body

weight and length and sex ratio differences were not evident among exposed groups compared with controls. Minor skeletal variations, primarily misaligned, fused or bipartite sternebrae, were increased among fetuses exposed on days 1-19 of gestation and may or may not have been exposure-related. Hackett et al. (1982) concluded that propylene-oxide caused maternal toxic effects, which contributed to embryotoxic effects and increased resorption rates; however, no major malformations were produced.

Based on the insufficient data from the NIOSH (Hackett et al., 1982) teratogenicity study, the EPA (Federal Register, 1984) proposed that additional teratogenicity testing be conducted.

5.4. OTHER REPRODUCTIVE EFFECTS

Additional data regarding the possible effects of propylene oxide on the reproductive ability of laboratory animals or humans were not located in the available literature cited in the Appendix.

5.5. CHRONIC TOXICITY

The carcinogenic bioassay of propylene oxide can be used to determine toxic effects in rats and mice following chronic inhalation of the compound (NTP, 1985). Groups of 50 animals of each sex of F344/N rats and B6C3F1 mice were exposed to propylene oxide (99.9% purity) in air at 0, 200 or 400 ppm (0, 475 or 950 mg/m^3) for 6 hours/day, 5 days/week for 103 weeks. In rats, mortality was comparable between controls and exposed groups, and terminal body weights of high-dose males (8%) and females (6%) were only slightly depressed. Mice were more sensitive to propylene oxide, with lower survival in both exposed groups compared with controls (42/50, 34/50, 29/50 in control, low-dose and high-dose males; 38/50, 29/50 and 10/50 in females). Terminal body weight of high-dose females was 10% below controls;

high-dose males had 22% lower body weights. Exposure-related, non-neoplastic lesions in rats included suppurative inflammation of the nasal cavity (7/50, 19/50 and 33/50 in controls, low-dose and high-dose males, 3/50, 5/50 and 20/50 among females) with epithelial hyperplasia and squamous metaplasia. In mice, chronic inflammation of the nasal cavity occurred in 1/50, 13/50 and 38/50 males treated at 0, 200 and 400 ppm, and among 0/50, 13/50 and 17/50 females. Hyperplasia and metaplasia were seen in low incidences among high-dose mice but were not prevalent. No other dose-related toxic effects were evident in mice or rats upon examination. Neoplastic changes in the nasal cavity were seen in high-dose rats (papillary adenoma, 5/100, males and females combined) and high-dose mice (nasal cavity hemangiomas or hemangiosarcomas, 15/100 among males and females combined), while no treatment-related neoplastic changes occurred among low-dose groups (see Section 5.1. and Table 5-2).

The 28-month inhalation study conducted by Dow Chemical Company (Reuzel and Kuper, 1983) can also be used to determine chronic toxic effects and effective levels of propylene oxide. Groups of 100 male and 100 female Wistar-derived rats were exposed to 0, 30, 100 or 300 ppm (0, 71, 238 or 713 mg/m^3) propylene oxide (6 hours/day, 5 days/week) for 123-124 weeks. Interim kills of 10 animals/sex and dose group were made at 12, 18 and 24 months. Slight weight reduction and increased mortality were seen in males and females exposed to propylene oxide at 300 ppm compared with controls. Nonneoplastic histopathological changes occurred in the nasal cavity, with olfactory epithelial degeneration and basal cell hyperplasia occurring frequently in high-dose males (21/63 and 24/63) and females (26/65 and 33/65). The incidence of these lesions among rats exposed at 100 ppm propylene oxide was slightly increased in males (10/62 and 8/62) and females (7/62 and 9/62) compared with controls (5/66 and 4/66 in males; 7/64 and 0/64 in females).

There was a dose-related increase in the severity of these nasal lesions among rats treated at the higher two dose levels compared with controls. Rats treated at 30 ppm propylene oxide showed no significant signs of toxicity compared with controls. No treatment-related, histopathological changes were seen in the lungs, trachea, liver, kidneys, spleen or other major organs/tissues.

In a chronic inhalation study conducted for NIOSH, Sprinz et al. (1982) exposed male cynomolgus monkeys, Macaca fascicularis, to 0, 100 and 300 ppm (0, 238 and 713 mg/m³) propylene oxide for 6 hours/day, 5 days/week for 24 months. Only two animals/dose group were exposed and necropsied. Because emphasis was placed on detecting peripheral and CNS damage, histopathological examinations were limited to the sciatic and ulnar nerves, spinal cord and ~19 regions of the brain. Sprinz et al. (1982) suggested that the propylene oxide-exposed monkeys had signs of axonal dystrophy in the medulla oblongata, but also noted a slight indication of this lesion in one of the control monkeys. Because of the small number of exposed animals and the apparent difficulty in histological preparation of nervous tissue, these data do not clearly demonstrate a chronic toxic effect of propylene oxide inhalation on the nervous system.

Rowe et al. (1956) exposed groups of rats (n=10/sex/dose level), guinea pigs (n=8/sex), rabbits (n=1/sex) and monkeys (1-2/dose level) to propylene oxide at 0, 102, 195 and 457 ppm (0, 242, 463 and 1086 mg/m³), 7 hours/day, 5 days/week, for up to 198 days. In rats, eye and nose irritation was noted, with increased mortality that was (due to pneumonia) and slightly depressed weight gain occurring in the high-dose group. No significant effects occurred among rats exposed at the lower two levels. Similarly, guinea pigs exposed at 457 ppm showed eye and nose irritation, pulmonary congestion,

slight depression of weight gain and slight fatty changes in the liver. No effects were reported among guinea pigs exposed at 195 or 102 ppm. In rabbits and monkeys, no adverse effects were observed in animals exposed at any of the three propylene oxide exposure levels.

The NTP (1985) conducted 13-week inhalation toxicity studies using F344/N rats and B6C3F1 mice to establish appropriate dose levels for the chronic carcinogenicity bioassay. Groups of 10 males and 10 females of each species were exposed to 0, 31, 63, 125, 250 and 500 ppm (0, 74, 150, 297, 594 and 1188 mg/m^3) for 6 hours/day, 5 days/week for the duration of the study. None of the animals died. Final mean body weights of rats and mice exposed at 500 ppm were depressed 7.4 and 5.3% lower in male and female rats, 12.9 and 14.6% lower in male and female mice, respectively. Gross and microscopic examination, including one section through the nasal turbinates of each animal, revealed no treatment-related pathological effects among rats or mice.

5.6. OTHER RELEVANT INFORMATION

The acute toxicity of propylene oxide in terms of lethality levels (LD_{50} or LC_{50}) has been determined for several animal species by various routes. Reviews of these data by Cavender (1983) and Bogyo et al. (1980) are summarized in Table 5-4.

Rowe et al. (1956) reported that a single oral dose of 300 mg propylene oxide/kg as a 10% olive oil solution was the maximum level causing no mortality among young adult rats (n=5/group). A dose of 1000 mg/kg caused 100% mortality. Groups of five female rats were also given 0.0, 100, 200 or 300 mg propylene oxide/kg, 5 days/week for 24 days (18 doses). No deaths occurred, but high-dose rats had slightly lower body weights and histological evidence of gastric irritation and slight liver damage.

TABLE 5-4

Acute Toxicity of Propylene Oxide*

Route	Species	Sex	Strain	LD_{50}/LC_{50}	Reference
Oral	rat	M	Wistar	1140 mg/kg	Smyth et al., 1941
Oral	rat	NR	NR	946 mg/kg	Smyth et al., 1969
Oral	rat	NR	NR	772 mg/kg	Smyth et al., 1970
Oral	guinea pig	M/F	NR	690 mg/kg	Smyth et al., 1941
Oral	rat	M/F	NR	530 mg/kg	Antonova et al., 1981
Oral	rat	NR	NR	380 mg/kg	Pugaeva, 1967
Oral	rat	NR	NR	550 mg/kg	Bukhalovskii, 1972
Oral	mouse	F	NR	630 mg/kg	Antonova et al., 1981
Oral	mouse	NR	NR	440 mg/kg	Pugaeva, 1967
Oral	guinea pig	F	NR	660 mg/kg	Antonova et al., 1981
Oral	rat	NR	NR	523 mg/kg	Weil et al., 1963
Inhalation	rat	NR	Sherman	>4000 ppm/4 hours (9502 mg/m^3)	Smyth and Carpenter, 1948
Inhalation	rat	M	NR	4000 ppm/4 hours (9502 mg/m^3)	Jacobsen et al., 1956

TABLE 5-4 (cont.)

Route	Species	Sex	Strain	LD_{50}/LC_{50}	Reference
Inhalation	mouse	F	NR	1740 ppm/4 hours (4133 mg/m³)	Jacobsen et al., 1956
Inhalation	guinea pig	F	NR	4000 ppm 4 hours (9502 mg/m³) (LC_{low})	Rowe et al., 1956
Inhalation	dog	M	beagle	2000 ppm/4 hours (4571 mg/m³) (LC_{low})	Jacobsen et al., 1956
Dermal	rabbit	NR	NR	≈1730 mg/kg	Smyth and Carpenter, 1948
Dermal	rabbit	NR	NR	1245 mg/kg	Smyth et al., 1969; Weil et al., 1963

*Source: Cavender, 1983; Bogyo et al., 1980

NR = Not reported

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Following short-term inhalation exposure to propylene oxide, Rowe et al. (1956) reported that no mortality occurred among female rats (n=10) or female guinea pigs (n=5) exposed at 2000 ppm (4751 mg/m³) for 7 hours. Exposure at 4000 ppm propylene oxide caused death in 4/10 and 10/10 rats after 2 and 7 hours of exposure, respectively, and in 2/5 guinea pigs exposed for 7 hours. Respiratory difficulty and pneumonia occurred among survivors and lasted for several days following exposure. Repeated exposure to propylene oxide at 457 ppm (1086 mg/m³), 7 hours/day, 5 days/week for up to 39 days (27 exposures) caused decreased growth rate in rates and guinea pigs, as well as histological changes in the alveoli and interstitial regions of the lungs.

The NTP (1985) conducted single-exposure and 12-day inhalation studies of propylene oxide using F344 rats and B6C3F1 mice of both sexes. Single 4-hour inhalation studies in rats were conducted at 1277, 2970, 3794 and 3900 ppm (3033, 7055, 9012 and 9264 mg/m³) propylene oxide, with mortality occurring in 0/10, 3/10, 8/10 and 6/10 males and females combined. Dyspnea and red discharge from the nose occurred among rats exposed at the highest three dose levels. Exposure levels in the 12-day study in rats were 47.2, 98.5, 196, 487 and 1433 ppm (112, 234, 466, 1157 and 3404 mg/m³) for 6 hours/day, 5 days/week. Toxic effects, including dyspnea, gasping, ataxia and hypoactivity, were seen only among rats of the high-dose group. One male rat of the high-dose group died during the study.

Single 4-hour inhalation studies in mice were conducted at exposure levels of 387, 859, 1102, 1277 or 2970 ppm (919, 2041, 2618, 3033 or 70 mg/m³) propylene oxide (NTP, 1985). Mortality among the exposure groups was 1/10, 0/10, 6/10, 7/10 and 10/10 for males and females combined. Acute toxic effects included dyspnea (all exposed groups), sedation (two highest

exposure levels) and lacrimation (highest dose group). During 12-day studies, mice were exposed at 20.1, 47.2, 98.5, 196 or 487 ppm (48, 112, 234, 466 or 1157 mg/m^3) 6 hours/day, 5 days/week, with dyspnea occurring in mice exposed at the two highest exposure levels, hypoactivity among high-dose mice, and slightly decreased final relative body weight among high-dose males and females.

In humans, acute exposure to propylene oxide has caused temporary corneal injury (McLaughlin, 1946) and contact dermatitis (Van Ketel, 1979).

6. AQUATIC TOXICITY

Few data are available regarding the toxic effects of propylene oxide on aquatic species. Bridie et al. (1979b) conducted toxicity tests on propylene oxide using goldfish, Carassius auratus, but tests were limited to 25 hours to preclude evaporative loss of the compound. The static 24-hour LC_{50} in goldfish was 170 mg propylene oxide/ℓ. Crews (1974) treated bluegill sunfish, Lepomis macrochirus, and mosquitofish, Gambusia affinis, to propylene oxide at 130-240 and 100-180 mg/ℓ, respectively, for 96 hours to determine lethality levels. In bluegills, no deaths occurred in groups exposed at ≤150 mg/ℓ and the 96-hour LC_{50} was 215 mg propylene oxide/ℓ. Mosquitofish were slightly more sensitive, with no deaths occurring among groups exposed at ≤130 mg/ℓ and the 96-hour LC_{50} being 141 mg/ℓ.

The marine-acclimated mullet, Mugil cephalus, was exposed to propylene oxide at 60-130 mg/ℓ (Crews, 1974). No deaths occurred among groups exposed to ≤80 mg propylene oxide/ℓ within 96 hours. The 96-hour LC_{50} value was determined to be 89 mg propylene oxide/ℓ.

Additional data regarding the toxic effects of chronic exposure to propylene oxide on aquatic organisms or effects on aquatic plants were not located in the available literature cited in the Appendix. Data regarding the accumulation of propylene oxide or residues in aquatic organisms were not located in the available literature cited in the Appendix.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The Occupational Safety and Health Administration (Code of Federal Regulations, 1981) established a permissible exposure level as a TWA at 100 ppm (240 mg/m³) propylene oxide. The ACGIH (1984) adopted a TWA-TLV of 20 ppm (50 mg/m³) for an 8-hour workday and 40-hour workweek. The TWA-TLV was recommended based on the lesser toxicity of propylene oxide in relation to ethylene oxide (ACGIH, 1980).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of propylene oxide were not located in the available literature cited in the Appendix.

8. RISK ASSESSMENT

The available toxicological data regarding propylene oxide indicate that the compound is a contact carcinogen in rodents, causing forestomach tumors following ingestion (Dunkelberg, 1982) and nasal tumors after inhalation exposure (NTP, 1985) (see Section 5.1.). A study by the Dow Chemical Company (Reuzel and Kuper, 1983) reported a slight increase in nasal and respiratory tumors and increased mammary tumors (females) among rats exposed to propylene oxide by inhalation for 20 months. In support of this positive carcinogenic response, two studies reported the production of injection site tumors following subcutaneous injection of propylene oxide in rats (Walpole, 1958) and mice (Dunkelberg, 1979, 1981). Propylene oxide has been shown to be a positive mutagen in microbial reverse-mutation assays (primarily a base-pair mutagen), Drosophila melanogaster and several in vitro mammalian cell assays (see Table 5-3).

Propylene oxide was not teratogenic following exposure of pregnant rats and rabbits by inhalation to 500 ppm (1188 mg/m³), for 7 hours/day during gestation (Hackett et al., 1982; Hardin et al., 1983b). Maternal toxicity, as evidenced by decreased food consumption and body weight gain, changes in relative organ weights and pulmonary inflammation, was reported for rats, but not rabbits. Reproductive performance of rat dams that were exposed before mating and during gestation was impaired as evidenced by decreased numbers of corpora lutea, implantation sites and live fetuses and increased numbers of resorptions. Fetoxicity in rats (reduced fetal size and weights, reduced ossification, increased incidence of wavy ribs) and rabbits (misaligned, fused or bipartite sternebrae) was also observed.

In addition to neoplastic effects, chronic inhalation exposure of animals to propylene oxide has also resulted in nonneoplastic toxic effects. In the NTP (1985) study, mice had dose-related decreased survival and reduced body weight gain at 200 and 400 ppm (475 and 950 mg/m³), 6 hours/day, 5 days/week for 103 weeks. Mice and rats had dose-related increased incidences and severity of suppurative inflammation of the nasal cavity; in rats, the inflammation was accompanied by epithelial hyperplasia and squamous metaplasia. Reuzel and Kuper (1983) found that rats treated at 100 and 300 ppm (238 and 713 mg/m³), 6 hours/day, 5 days/week for 28 months had olfactory epithelial degeneration and basal cell hyperplasia in the nasal cavity. No effects were observed at 30 ppm (71 mg/m³). Rowe et al. (1956) found no adverse effects in rabbits or monkeys exposed by inhalation to propylene oxide at ≤457 ppm (1086 mg/m³), 7 hours/day, 5 days/week for 198 days. Rats and guinea pigs, however, had eye and nose irritation, decreased weight gain, increased mortality (rats), pulmonary congestion (guinea pigs) and fatty changes in the liver (guinea pigs) at 457 ppm, but not at ≤195 ppm (≤463 mg/m³). Although 30 ppm (71 mg/m³), 6 hours/day, 5 days/week (Reuzel and Kuper, 1983) appears to be the NOEL for nonneoplastic effects, because of the demonstrated carcinogenicity of propylene, it is appropriate to derive a q_1^*.

The oral (gavage) administration study by Dunkelberg (1982) and the inhalation bioassay by the NTP (1985) would be appropriate for unit risk estimation for the carcinogenicity of propylene oxide. The study by Dunkelberg (1982) demonstrated a dose-related tumor response with a significantly increased incidence of forestomach squamous-cell carcinoma among rats exposed at 60 mg/kg (19/50) compared with controls (0/100 for combined vehicle and untreated controls (see Table 5-1). Groups of 50 female

Sprague-Dawley rats were exposed at 0.0, 15 or 60 mg/kg for 219 days during the 150-week study, giving average total doses of 0, 2714 or 10,798 mg/kg, respectively. Although this study used only female Sprague-Dawley rats, there is no indication from the NTP (1985) data that propylene oxide is a sex-specific tumorigen. Using the average total doses administered during the 150-week (1050 day) study, transformed dose levels were determined to be 0.0, 2.58 and 10.28 mg/kg/day. The incidence of forestomach squamous-cell carcinoma was 0/100, 2/50 and 19/50, respectively, for controls (combined vehicle and untreated controls), low-dose and high-dose groups. The q_1^* values were calculated using the linearized multistage model developed by Kenneth Crump and adopted by the U.S. EPA (Federal Register, 1980). The q_1^* for the experimental animals calculated from these data is 4.08×10^{-2} $(mg/kg/day)^{-1}$. The human q_1^* is 2.39×10^{-1} $(mg/kg/day)^{-1}$ after adjusting for human and experimental animal body weights [q_1^* for humans = (q_1^* for animals)(70 kg/0.35 kg)$^{1/3}$] (Table 8-1).

In comparison, tumor incidence data reported by the NTP (1985) can be used for carcinogenicity risk estimation, but leads to a lower, less conservative q_1^* value. Groups of 50 male and female F344 rats and B6C3F1 mice were exposed to propylene oxide by inhalation at 0, 200 and 400 ppm (0, 475 and 950 mg/m^3), 6 hours/day, 5 days/week for 103 weeks. The incidence of papillary adenoma in the nasal cavity of rats exposed at the highest dose level was 2/50 for males and 3/50 for females, which suggests a carcinogenic response; however, these incidences are not significantly increased compared with controls (0/50 for both sexes) and are inappropriate for carcinogenicity risk estimation. In mice, the incidence of nasal cavity hemangioma or hemangiosarcoma was 10/50 and 5/50, respectively, in the high-dose males ($p=0.001$) and females ($p=0.028$). These data show that the nasal cavity is

TABLE B-1

Cancer Data Sheet for Derivation of q_1^*

Compound: Propylene oxide

Reference: Dunkelberg, 1982

Species, Strain, Sex: rat/Sprague-Dawley/female

Body weight: 0.35 kg (assumed)

Length of exposure (le) = 1029 days

Length of experiment (Le) = 1050 days

Lifespan of animal (L) = 1050 days

Tumor site and type: forestomach squamous-cell carcinoma

Route, vehicle: oral, Livio salad oil

Experimental Doses or Exposures (mg/kg/day)	Transformed Dose* (mg/kg/day)	Incidence: No. Responding/No. Tested or Examined
60 (219 exposures; total dose 2714 mg/kg)	10.28	19/50
15 (219 exposures; total dose 2714 mg/kg)	2.58	2/50
0.0 (combined vehicle and untreated control)	0.0	0/100

*See text for calculation of transformed dose.

Unadjusted q_1^* from study = 4.0807665×10^{-2} $(mg/kg/day)^{-1}$
Human q_1^* = 2.39×10^{-1} $(mg/kg/day)^{-1}$

the primary target area of propylene oxide carcinogenesis following inhalation and demonstrate that the compound is a contact carcinogen. The exposure level and incidence of nasal cavity hemangioma or hemangiosarcoma among male mice (0/50, 0/50 and 10/50 among control, low-dose and high-dose) can be used for the derivation of a q_1^*. Based on the experimental exposure levels of 0, 200 and 400 ppm (0, 475 and 950 mg/m^3) and treatment duration (6 hours/day, 5 days/week for 721 days), transformed dose levels of 0.0, 55 and 110 mg/kg/day were determined assuming 50% pulmonary absorption, 0.030 kg mouse body weight and 0.039 m^3/day as the daily inhalation volume for mice. The transformed dose levels and tumor response data can be used in the multistage model to estimate a q_1^* for experimental animals. These data result in a q_1^* for animals of 9.84×10^{-4} $(mg/kg/day)^{-1}$. The human q_1^* was determined to be 1.31×10^{-2} $(mg/kg/day)^{-1}$ after adjusting for human and experimental animal body weight differences (Table 8-2).

The q_1^* for human carcinogenic risk following exposure to propylene oxide is 2.39×10^{-1} $(mg/kg/day)^{-1}$. This value determined from the Dunkelberg (1982) study is ~20-fold higher than that derived from the NTP (1985) data and is therefore selected as the most protective human carcinogenic potency factor for propylene oxide.

TABLE 8-2

Cancer Data Sheet for Derivation of q_1^*

Compound: Propylene oxide

Reference: NTP, 1985

Species, Strain, Sex: mice/B6C3F1/male

Body weight: 0.03 kg (assumed)

Length of exposure (le) = 721 days

Length of experiment (Le) = 721 days

Lifespan of animal (L) = 721 days

Tumor site and type: nasal cavity hemangioma or hemangiosarcoma

Route, vehicle: inhalation

Experimental Doses or Exposures (mg/kg/day)	Transformed Dose* (mg/kg/day)	Incidence: No. Responding/No. Tested or Examined
400 ppm x 6 hours/day x 5 days/week	110	10/50
200 ppm x 6 hours/day x 5 days/week	55	0/50
0.0 ppm	0.0	0/50

*See text for calculation of transformed dose.

Unadjusted q_1^* from study = 9.8397111×10^{-4} $(mg/kg/day)^{-1}$
Human q_1^* = 1.31×10^{-2} $(mg/kg/day)^{-1}$

9. REPORTABLE QUANTITY

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

The available data regarding the toxic effects of propylene oxide following chronic exposure were reviewed in Section 5.5. In addition, two teratogenicity studies were available (see Section 5.3.). Several studies reported sufficient data for the derivation of a human MED, CS and RQ (Table 9-1). Data are available only for inhalation exposure to propylene oxide. To calculate the MEDs, inhalation exposures were expanded from intermittent to continuous and multiplied by the animal breathing rate and the cube root of the ratio of the animal weight to human weight and divided by the animal weight. The subsequent value is multiplied by 70 kg to put the MED in units of mg/day for a 70 kg man.

The NTP (1985) reported that nasal cavity inflammation and epithelial hyperplasia and metaplasia were increased in rats exposed at 200 ppm propylene oxide (6 hours/day, 5 days/week) for 103 weeks. In mice, exposure at 200 ppm caused similar effects in the nasal cavity and also increased the rate of mortality among males and females. Based on the animal exposure level of 200 ppm (475 mg/m^3) and the dosing schedule (6 hours/day, 5 days/week), a human MED of 650 and 597 mg/day were determined for rats and mice (see Table 9-1). The resulting RV_d for rats and mice was 1.3. Effects noted in rats and mice at the 200 ppm exposure level warrant RV_es of 5 and 10, respectively. The corresponding CS and RQ values based on effects in rats would be 6.5 and 1000, and those derived from effects in mice would be 13 and 1000, respectively.

Reuzel and Kuper (1983) exposed male and female rats to propylene oxide by inhalation at 0, 30, 100 and 300 ppm (6 hours/day, 5 days/week) for up to 123-124 weeks. No toxic effects were noted in rats treated at 30 ppm, while cytotoxic effects of the nasal cavity occurred among rats exposed at 100 and

TABLE 9-1

Composite Scores for Chronic Inhalation Toxicity of Propylene Oxide

Species	Animal Exposure	Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Rat	200 ppm (475 mg/m³), 6 hours/day, 7 days/ week for 103 weeks	650	1.3	Nasal inflammation, hyperplasia and metaplasia	5	6.5	1000	NTP, 1985
Mouse	200 ppm (475 mg/m³), 6 hours/day, 5 days/ week for 103 weeks	597	1.3	Increased mortality; nasal inflammation	10	13	1000	NTP, 1985
Rat	100 ppm (238.5 mg/m³), 6 hours/day, 5 days/ week for 123 weeks	325	1.7	Nasal epithelial degeneration and basal cell hyperplasia	5	8.5	1000	Reuzel and Kuper, 1983
Rat	300 ppm (713.6 mg/m³), 6 hours/day, 5 days/ week for 123 weeks	976	1.0	Increased mortality; nasal epithelial degeneration and basal cell hyperplasia	10	10	1000	Reuzel and Kuper, 1983
Rat	457 ppm (1084 mg/m³), 7 hours/day, 5 days/ week, 112 days (males) 198 days (females)	1730	1.0	Increased mortality due to pneumonia; nasal and eye irritation	10	10	1000	Rowe et al., 1956
Guinea pig	457 ppm (1084 mg/m³), 7 hours/day, 5 days/ week, 157 days	583	1.4	Pulmonary congestion, fatty degeneration of liver; eye and nasal irritation	5	7	1000	Rowe et al., 1956
Rat	500 ppm (1188 mg/m³), 7 hours/day, prior to and during gestation	2655	1.0	Reduced reproductive capacity, fetotoxicity and maternal toxicity	9	9	1000	Hardin et al., 1983b; Hackett et al., 1982

300 ppm. Nasal epithelial degeneration and basal cell hyperplasia occurred in rats exposed at 100 and 300 ppm with incidence and severity increased at the higher dose level. Mortality among rats of both sexes exposed at 300 ppm was also increased compared with controls. The animal exposure levels of 100 and 300 ppm (238.5 and 713.6 mg/m³; 6 hours/day, 5 days/week) were used to determined human MED levels of 325 and 976 mg/day, respectively, and RV_d values of 1.7 and 1.0. The effects on the nasal cavity of rats exposed at 100 ppm require an RV_e of 5, while increased mortality noted among rats exposed at 300 ppm require an RV_e of 10 (see Table 9-1). The CS and RQ values based on chronic toxic effects in rats exposed at 100 ppm were 8.5 and 1000, while those in rats exposed at 300 ppm propylene oxide were 10 and 1000, respectively.

Toxicity studies conducted by Rowe et al. (1952) demonstrated eye and nasal irritation and increased mortality that was due to pneumonia among male and female rats exposed at 457 ppm propylene oxide (7 hours/day, 5 days/week) for 112 days (males) and 198 days (females). In guinea pigs exposed at the same level and on the same schedule for 157 days, eye and nose irritation, histological pulmonary irritation and fatty degeneration of the liver were observed. Although the durations of these studies were not exceedingly long, they do represent a substantial portion of the lifespan of rats and guinea pigs and, therefore, will be considered chronic exposures. The animal exposure level of 457 ppm (1084 mg/m³) for 7 hours/day, 5 days/week results in human MED level of 1730 and 583 mg/day. The appropriate RV_d values for these human MEDs would be 1.0 and 1.4. In rats, the increased mortality from pneumonia (presumed to be induced by propylene oxide inhalation) requires an RV_e of 10. The resulting CS and RQ based on the toxicity of propylene oxide in rats would be 10 and 1000,

respectively (see Table 9-1). Toxic effects seen in guinea pigs warrant an RV_e value of 5. The CS and RQ for toxic effects in guinea pigs are 7 and 1000, respec- tively (see Table 9-1).

In a combined teratogenicity/reproduction study (Hackett et al., 1982; Hardin et al., 1983b), rats and rabbits were exposed by inhalation to 500 ppm propylene oxide, 7 hours/day. Four groups of rats were studied: group 1 was the control, group 2 was exposed on days 7-16 of gestation, group 3 was exposed on days 1-16 of gestation and group 4 was exposed 5 days/week for 3 weeks before mating, followed by days 1-16 of gestation. Rabbits were exposed on days 7-10 or 1-19 of gestation. In rats, maternal toxicity (changes in organ weights, pulmonary inflammation) and fetotoxicity (reduced fetal weight and length, increased incidence of wavy ribs, delayed ossification) were observed in all treated groups. In group 4, reproductive capacity was impaired as evidenced by decreased numbers of corpora lutea, implantation sites and live fetuses. Groups 2 and 3 had increased numbers of resorptions. In rabbits, the only effects observed were minor skeletal variations in fetuses, which may or may not have been treatment-related. No teratogenic effects were evident in rats or rabbits. Using the exposure level of 500 ppm (1188 mg/m³), 7 hours/day, a human MED of 2655 mg/day and an RV_d of 1 was determined. The highest RV_e that can be assigned is 9, based on the impaired reproductive capacity of rats. The CS is 9 and the RQ is 1000.

A review of the toxicity data of propylene oxide following inhalation exposure (see Table 9-1) indicates that nasal inflammation with possible hyperplasia and metaplasia are the major effects in rodents exposed at levels of 100-200 ppm (6-7 hours/day, 5 days/week). In addition to cytotoxic effects in the nasal cavity, increased mortality was reported among

mice exposed at 200 ppm (6 hours/day, 5 days/week) for 103 weeks (NTP, 1985) and in rats exposed at 300 ppm (6 hours/day, 5 days/week) for 123-124 weeks (Reuzel and Kuper, 1983). The chronic toxicity data (NTP, 1985) of mice exposed to propylene oxide at 200 ppm for 103 weeks lead to the most conservative CS and RQ values (13 and 1000, respectively) and are, therefore, selected as the most appropriate representation of the toxic potency of this compound (Table 9-2).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

The carcinogenicity of propylene oxide has been tested following oral administration, inhalation and subcutaneous injection in rats and mice. These data demonstrate that propylene oxide is a contact carcinogen, which produces forestomach tumors following oral administration, nasal tumors following inhalation and subcutaneous tumors after subcutaneous injection. Dunkelberg (1982) administered propylene oxide to female Sprague-Dawley rats by gavage. Histopathological examinations revealed a high incidence of forestomach tumors, primarily squamous-cell carcinoma among propylene oxide-treated rats (see Table 5-1).

In the recently completed NTP (1985) inhalation bioassay of propylene oxide, the tumor response in rats suggested that propylene oxide affected the nasal epithelium since papillary adenomas of the nasal turbinates were reported. No nasal tumors were observed among low-dose or control group rats (see Table 5-2). In mice, several types of nasal tumors occurred among high-dose males and females. Nasal adenocarcinoma and nasal hemangioma or hemangiosarcoma occurred in high-dose male and female mice. The incidence of nasal hemangioma and hemangiosarcoma in high-dose male (10/50, p=0.001) and female mice (5/50, p=0.028) compared with controls (0/50) clearly demonstrates the carcinogenicity of propylene oxide to the nasal cavity following chronic inhalation (see Table 5-2).

TABLE 9-2

Propylene oxide

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose*:	848 mg/day
Effect:	increased mortality; nasal inflammation
Reference:	NTP, 1985
RV_d:	1.3
RV_e:	10
Composite Score:	13
RQ:	1000

*Equivalent human dose

Suggestive evidence of the carcinogenicity of propylene oxide was shown in the 28-month inhalation study by Reuzel and Kuper (1983) (see Section 5.1.). The nasal cavity was the major target organ with epithelial hyperplasia and degeneration occurring, and single cases of nasal squamous-cell carcinoma, tracheal squamous-cell carcinoma, laryngopharyngeal squamous-cell carcinoma and adenocarcinoma of the laryngopharynx reported among high-dose group rats. No similar tumors occurred among rats exposed at lower propylene oxide levels or among controls. The incidence of mammary tumors (malignant and benign) among female rats, both the number of rats with tumors and the average number of tumors/animal increased with dose and was suggested as being a treatment-related tumorigenic response.

Subcutaneous injection studies by Walpole (1958) and Dunkelberg (1979, 1981) demonstrated a dose-related increase in subcutaneous sarcomas at the injection site among rats and mice (see Section 5.1.).

In addition to the available positive carcinogenicity data for propylene oxide, the compound has been demonstrated as a positive mutagen in a number of assay systems (see Table 5-3) including several in vitro studies using cultured mammalian cells.

There is sufficient evidence from the available carcinogenicity bioassays of propylene oxide to regard the compound as a positive animal carcinogen following oral or inhalation exposure. Propylene oxide appears to be a contact carcinogen, affecting the tissue first contacted following exposure. The lack of data on humans exposed to propylene oxide precludes an evaluation of its carcinogenicity for humans; however, the CAG (1979) considers propylene oxide a possible human carcinogen. Thus, using the EPA (1984) guidelines for evaluating the overall weight of evidence of carcinogenicity to humans, propylene oxide is most appropriately classified as a

group B2 chemical. The most appropriate data for the determination of a F-factor for propylene oxide are those for the development of forestomach squamous-cell carcinoma among female rats treated orally for up to 150 weeks (Dunkelberg, 1982). The effective transformed dose is lower and the tumor incidence data are higher in the Dunkelberg (1982) study compared with the data from the NTP (1985) inhalation study (see Chapter 8); therefore, a higher, more conservative potency estimate of propylene oxide would result. A summary of the data from the Dunkelberg (1982) study and the derivation of the F factor is presented in Table 9-3. The F-factor was determined to be 1.30, which places propylene oxide in potency group 3, having a "low" hazard ranking according to the scheme established by the Carcinogen Assessment Group (U.S. EPA, 1984).

TABLE 9-3

Derivation of Potency Factor (F)
Agent: Propylene Oxide

Reference:	Dunkelberg, 1982		
Exposure route:	oral		
Species:	rat		
Strain:	Sprague-Dawley		
Sex:	female		
Vehicle or physical state:	salad oil		
Body weight[a]:	0.35 kg		
Duration of treatment:	1029 days		
Duration of study:	1050 days		
Lifespan of animal:	1050 days		
Target organ:	forestomach		
Tumor type:	squamous-cell carcinoma		
Experimental doses/ exposure:	60 mg/kg/219 (10,798 mg/kg total dose)[b]	15 mg/kg/219 (2714 mg/kg total dose)[b]	0.0 mg/kg
Transformed doses (mg/kg/day):	10.28	2.58	0.0
Tumor incidence:	19/50	2/50	0/100[c]
Unadjusted $1/ED_{10}$:	2.225389		
F factor:	1.30		

[a]estimated

[b]reported total doses used to calculate transformed dose (total dose/total days of study)

[c]combined vehicle and untreated control groups

10. REFERENCES

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in November 1984 with the exception of the TOXLINE, which was searched in July 1984 and kindly supplied by Dynamac Corporation. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1983. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1983-1984. Cincinnati, OH. 94 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-83. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technology Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1984. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, I.N. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1984. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1982. Chemical Activities Status Report, 3rd ed. (EPACASR). Offices of Pesticides and Toxic Substances, Washington, DC. EPA 560/TIIS-82-002b.

U.S. EPA. 1983. Status Report on Rebuttable presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1984. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422. Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. USDI, Fish and Wildlife Service Resource Publ. 137. Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California. State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. PB-269605. Prepared for the U.S. EPA, Washington, DC.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.